

Claims

1. A fusion protein comprising an interferon-alpha (IFN- α) molecule joined at its C terminal end through a peptide linker to an N terminal end of an immunoglobulin heavy chain comprising a hinge, C_H2, and C_H3 domain, wherein the linker has a sequence chosen from
5 Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (GS10; SEQ ID NO:28), Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (GS15; SEQ ID NO:29), and Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (GS20; SEQ ID NO:30).
- 10 2. The fusion protein of claim 1, wherein the IFN- α is IFN- α 2b.
3. The fusion protein of claim 1, wherein the IFN- α is a consensus IFN.
4. The fusion protein of claim 1, wherein the immunoglobulin heavy chain is a human
15 Fc γ 1 heavy chain.
5. The fusion protein of claim 1, wherein the immunoglobulin heavy chain has an amino acid sequence provided by SEQ ID NO:2.
- 20 6. The fusion protein of claim 1, wherein the IFN- α is IFN- α 2b and the immunoglobulin heavy chain is a human Fc γ 1 heavy chain.
7. The fusion protein of claim 1, wherein the linker has a sequence Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (GS10; SEQ ID NO:28).
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8. The fusion protein of claim 1, wherein the linker has a sequence Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (GS15; SEQ ID NO:29).
9. The fusion protein of claim 1, wherein the linker has a sequence Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (GS20; SEQ ID
30 NO:30).

10. The fusion protein of claim 1, wherein the fusion protein is a disulfide-linked homodimer.
11. A fusion protein comprising an interferon-alpha 2b (IFN- α 2b) molecule joined at its
5 C terminal end through a peptide linker to an N terminal end of a human Fc γ 1 heavy chain comprising a hinge, C_H2, and C_H3 domain, wherein the linker has a sequence Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (GS15; SEQ ID NO:29).
12. The fusion protein of claim 1, wherein the fusion protein is a disulfide-linked
10 homodimer.
13. A method for systemic delivery of interferon-alpha (IFN- α), comprising:
administering an effective amount of an aerosol of a fusion protein of claim 1 to lung
such that a central lung zone/peripheral lung zone deposition ratio (C/P ratio) is at least 0.7.
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14. The method of claim 13, wherein the C/P ratio is at least 1.0.
15. The method of claim 13, wherein the C/P ratio is at least 1.5.
- 20 16. The method of claim 13, wherein the C/P ratio is at least 2.0.
17. The method of claim 13, wherein the fusion protein is a disulfide-linked homodimer.
18. A method for systemic delivery of interferon-alpha 2b (IFN- α 2b), comprising:
25 administering an effective amount of an aerosol of a fusion protein of claim 11 to lung
such that a central lung zone/peripheral lung zone deposition ratio (C/P ratio) is at least 0.7.
19. The method of claim 18, wherein the C/P ratio is at least 1.0.
- 30 20. The method of claim 18, wherein the C/P ratio is at least 1.5.
21. The method of claim 18, wherein the C/P ratio is at least 2.0.

22. The method of claim 18, wherein the fusion protein is a disulfide-linked homodimer.
23. A method for systemic delivery of interferon-alpha (IFN- α), comprising:
5 administering an effective amount of an aerosol of a fusion protein of claim 1 to lung,
wherein particles in the aerosol have a mass median aerodynamic diameter (MMAD) of at
least 3 micrometers (μm).
24. The method of claim 23, wherein the MMAD of the particles is between 3 μm and
10 about 8 μm .
25. The method of claim 23, wherein the MMAD of the particles is greater than 4 μm .
26. The method of claim 23, wherein a majority of the particles are non-respirable.
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27. The method of claim 23, wherein the fusion protein is a disulfide-linked homodimer.
28. A method for systemic delivery of interferon-alpha 2b (IFN- α 2b), comprising:
administering an effective amount of an aerosol of a fusion protein of claim 11 to
20 lung, wherein particles in the aerosol have a mass median aerodynamic diameter (MMAD) of
at least 3 micrometers (μm).
29. The method of claim 28, wherein the MMAD of the particles is between 3 μm and
about 8 μm .
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30. The method of claim 28, wherein the MMAD of the particles is greater than 4 μm .
31. The method of claim 28, wherein a majority of the particles are non-respirable.
- 30 32. The method of claim 28, wherein the fusion protein is a disulfide-linked homodimer.
33. An aerosol delivery system, comprising a container, an aerosol generator connected to

the container, and a fusion protein of claim 1 disposed within the container, wherein the aerosol generator is constructed and arranged to generate an aerosol of the fusion protein having particles with a MMAD of at least 3 μm .

5 34. The aerosol delivery system of claim 33, wherein the MMAD of the particles is greater than 4 μm .

35. The aerosol delivery system of claim 33, wherein a majority of the particles are non-respirable.

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36. The aerosol delivery system of claim 33, wherein the aerosol generator comprises a vibrational element in fluid connection with a solution containing the fusion protein.

37. The aerosol delivery system of claim 33, wherein the aerosol generator is a nebulizer.

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38. The aerosol delivery system of claim 33, wherein the aerosol generator is a mechanical pump.

39. The aerosol delivery system of claim 33, wherein the container is a pressurized
20 container.

40. An aerosol delivery system, comprising a container, an aerosol generator connected to the container, and a fusion protein of claim 11 disposed within the container, wherein the aerosol generator is constructed and arranged to generate an aerosol of the fusion protein
25 having particles with a MMAD of at least 3 μm .

41. The aerosol delivery system of claim 40, wherein the MMAD of the particles is greater than 4 μm .

30 42. The aerosol delivery system of claim 40, wherein a majority of the particles are non-respirable.

43. The aerosol delivery system of claim 40, wherein the aerosol generator comprises a vibrational element in fluid connection with a solution containing the fusion protein.
44. The aerosol delivery system of claim 40, wherein the aerosol generator is a nebulizer.
- 5 45. The aerosol delivery system of claim 40, wherein the aerosol generator is a mechanical pump.
46. The aerosol delivery system of claim 40, wherein the container is a pressurized
- 10 container.
47. A method of treating an interferon-alpha (IFN- α)-sensitive disease in a subject, comprising
- administering to a subject having an IFN- α -sensitive disease an aerosol of the fusion
- 15 protein of claim 1, in an effective amount to treat the IFN- α -sensitive disease.
48. The method of claim 47, wherein the IFN- α -sensitive disease is chosen from hairy cell leukemia, AIDS-related Kaposi's sarcoma, chronic phase Philadelphia chromosome-positive chronic myelogenous leukemia, malignant melanoma, follicular lymphoma,
- 20 condylomata acuminata, chronic hepatitis C, and chronic hepatitis B.
49. A method of treating an interferon-alpha 2b (IFN- α 2b)-sensitive disease in a subject, comprising
- administering to a subject having an IFN- α 2b-sensitive disease an aerosol of the
- 25 fusion protein of claim 11, in an effective amount to treat the IFN- α 2b-sensitive disease.
50. The method of claim 49, wherein the IFN- α 2b-sensitive disease is chosen from hairy cell leukemia, malignant melanoma, follicular lymphoma, condylomata acuminata, AIDS-related Kaposi's sarcoma, chronic hepatitis C, and chronic hepatitis B.